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The Asymmetric Synthesis of Novel Tin-Functionalized Carbapenam Systems Through Radical Cyclization of Enyne β-Lactams

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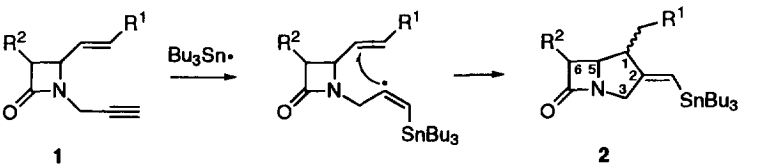
Abstract.- New chiral, non-racemic, vinylstannyl carbapenams **2** are easily accessible by the regio- and stereocontrolled tin-mediated, vinyl radical intramolecular cyclization of enyne β-lactams **1**.

The cyclization of enynes promoted by an external radical source is an elegant and efficient methodology to build bi- and polycyclic systems with good levels of both regio- and stereoselectivity.[1] However, the use of this approach in the synthesis of fused bicyclic β-lactams is limited to the cyclization of *N*-(2-bromo-2-propen-1-yl)-4-vinyl-2-azetidinone to yield both carbapenam and carbacepham derivatives.[2] In fact, although numerous routes to fused bicyclic β-lactams through radical ring closure are known, most of them make use of halogen-, thio-, and seleno-derivatives as pro-radical centers.[3] Generation of the radical by some of the standard methodologies and its intramolecular capture by a radical acceptor attached to the 2-azetidinone nucleus results in ring closure. Easily available *N*-(prop-2-ynyl)-2-azetidinones of type **1** have been introduced recently by us[4] as intermediates in the synthesis of *N*-unsubstituted-β-lactams *via* a Nicholas-type reaction of their hexacarbonyl-dicobalt complexes. It is clear that the terminal alkyne on compounds **1** can act as pro-radical center[5] and, provided that a radical acceptor is present at C3, these compounds can be used in the preparation of bicyclic-β-lactams (Scheme 1). We describe here the development of this methodology as an efficient approach to the asymmetric synthesis of the previously unknown stannyl carbapenams, **2**.[6]

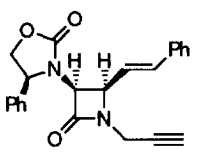


1 **2**

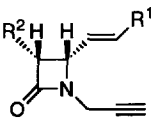
Scheme 1

Two complementary asymmetric approaches to 2-azetidinones **1** were used. Enantiomerically pure 2-azetidinone **1a** was obtained from (+)-(*S*)-(4-phenyl-2-oxo-1,3-oxazolidin-3-yl)acetic acid and the imine derived from propargylamine and cinnamaldehyde in the presence of dichlorophenylphosphate as condensating agent.[7] Optically pure compounds **1b-d** were conveniently prepared from (+)-(3*R*, 4*S*,4'*S*)-2-azetidinones **3**[8]

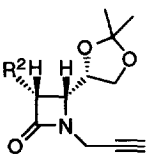
by chemical elaboration of the side chain at C4. Standard acetonide hydrolysis in **3** followed by $NaIO_4$ cleavage of the corresponding diols in MeOH/H_2O gave the expected 4-formyl-2-azetidinones as inseparable mixtures with their methoxy hemiacetals. Wittig olefination of the corresponding mixtures furnished the desired enyne-β-lactams **1b-d** in excellent yields.[9]



1a



1b: R^1 = Ph, R^2 = PhO
1c: R^1 = CO_2Me, R^2 = PhO
1d: R^1 = Ph, R^2 = BnO



3a : R^2 = PhO
3b : R^2 = BnO

Treatment of the enyne β-lactams **1a-d** with tributyltin hydride and AIBN gave the expected carbapenams **2a-d** having an exocyclic vinyltin in high yields after chromatographic separation (Scheme 2, Table).[10, 11] The cyclization process was totally regioselective in all the cases tested. The products were formed by a 5-*exo-trig* radical process which is known to be preferred when the radical acceptor has a radical-stabilizing substituents at the β-position (in our case the styryl and the α,β-unsaturated ester groups).[12]

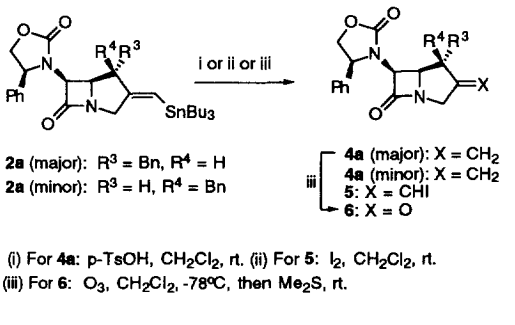
Table. Synthesis of 2-Stannylmethylenecarbapenams **2** from Enyne β-Lactams **1**

entry	substrate[b]	R^1	R^2	product	isomer ratio[c]	yield (%)[a] *major*	*minor*
1	**1a**	Ph	*S*-Ox[d]	**2a**	88:12	80	11
2	**1b**	Ph	PhO	**2b**[e]	81:19	41 (66)	-
3	**1c**	CO_2Me	PhO	**2c**	85:15	58	12
4	**1d**	Ph	BnO	**2d**[f]	85:15	- (71)	10

a In all cases complete transformation into the bicyclic products was observed by ^{1}H-NMR. Yields without parenthesis are pure, isolated product by column chromatography. Those within parenthesis are for the mixture of both unseparable isomers. With exception of **2a**, partial destannylation and/or decomposition was observed after chromatographic workup. *b* Except for enyne β-lactam **1a** (*E*-isomer), *E/Z* mixtures of isomers were used for **1b** (76/24), **1c** (86/14) and for **1d** (52:48). *c* Isomer ratios (epimers at C1) were determined by integration of well-resolved signals in the ^{1}H-nmr spectra of crude reaction mixtures. *d* *S*-Ox = *(S)*-4-phenyl-2-oxo-1,3-oxazolidin-3-yl. *e* Attempts to isolate the minor isomer were unsuccesful in this case. *f* Attempts to isolate the major isomer were unsuccesful in this case.

Vinylstannyl derivatives **2** were obtained as mixtures of two diastereomers (epimers at C1)[13] with good diastereoselectivity (Table). The isomer ratio is remarkably independent of the stereochemistry of the double bond at C4 of the 2-azetidinone ring.[14] The relative stereochemistry of the 4-membered ring is easily established from ^{1}H NMR data based on the values of $J_{5,6}$, and is transferred unaltered from the starting 2-azetidinone to the cyclised products. However, the stereochemistry of the new chiral center at C1 could not be determined in the same way.[15] Destannylation of the major isomer of compound **2a** afforded methylenecarbapenam **4a** from which adequate crystals could be grown and hence the configuration resolved by X-ray crystallographic analysis (Scheme 2 and Figure). From these results it is reasonable to assume that the

configuration at C1 of all major isomers should be the same. The slight variation of the stereochemical outcome of the reactions tested independently of the nature of the substituents R^1 and R^2 support this hypothesis.



Scheme 2

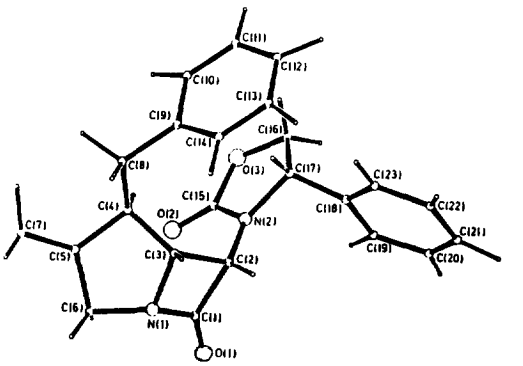


Figure. Crystal structure of **4a** (major)

The above method is an easy entry to the hitherto unknown, 2-stannylmethylene carbapenams **2**. These interesting compounds can be transformed to different compounds lacking the metallic moiety. Thus, for example, in addition to the easy protiodestannylation to 2-methylenecarbapenams under acidic conditions, compound **2a** can undergo electrophilic iodine substitution to 2-iodomethylenecarbapenam **5**, or ozonolysis to give 2-oxocarbapenam **6** (Scheme 2). The latter compound can be also obtained from 2-methylenecarbapenam **4a**. Finally, stannyl derivatives **2** are useful vinyl carbanion equivalents,[16] or may be functionalized using conventional Pd(0) chemistry.[17, 18]

In conclusion, the methodology outlined in Scheme 1 provides a direct method for the stereoselective asymmetric synthesis of novel tin-functionalized carbapenams **2**. Work to determine the scope of this new synthetic strategy and to use the stannylcarbapenams in the synthesis of bicyclic β-lactam antibiotics is now underway in our laboratory.

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9. Compounds **1b-d** were obtained as mixtures of E/Z isomers across the double bond having the same *cis*-configuration in the β-lactam ring.
10. A typical experimental procedure follows. A solution of enyne-β-lactam **1** (1mmol), Bu_3SnH (1.15 mmol), and AIBN (0.1 mmol) was refluxed in dry benzene (20 mL) under an argon atmosphere, until complete disappearance of the starting substrate (t.l.c.). The solvent was evaporated *in vacuo* to give an oil which was purified by flash chromatography. In all the cases, major isomer was eluted first. In some cases partial destannylation and/or decomposition was observed, specially in the 6-alkoxycarbapenams. Complete separation and/or purification of both diastereomers was not possible in these cases. All pure compounds gave satisfactory spectroscopic and analytical data.
11. It is notable that radical cyclization to give carbapenams **2** occurs under standard conditions while related processes developed to prepare bicyclic β-lactams do not occur except in high dilution conditions. See, for example ref. 3. In our case, good yields of compounds **2** were obtained even when working in the absence of solvent (neat conditions).
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13. To determine the nature of both isomers obtained in the cyclization of 2-azetidinones **1** (epimers at C1 or *E/Z* isomers in the olefinic double bond), the isolated isomers of compound **1a** were treated with TsOH. Two new carbapenams, **4a**, lacking the tin moiety were obtained. Therefore, both isomers of **2a** should have the same stereochemistry in the double bond but are epimers at C1. Moreover, according with previous background (see ref. 1) for cyclization of enynes it may be assumed that the double bond has a *Z*-stereochemistry.
14. The same yield and stereochemical result was obtained starting both with a mixture of *E/Z*-**1c** (85/15) and pure isomer *Z*-**1c**.
15. Major isomers of carbapenams **2** show a $J_{1,5}$ = 7.4-8.4 Hz while the minor isomers have a $J_{1,5}$ = 8.0 - 8.7 Hz. Therefore, relative configuration at C1 could not be unambiguously established from NMR data.
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